2022

The impact of acute stress and childhood traumatic events on pain sensitivity among adults with chronic low back pain

BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Thesis

THE IMPACT OF ACUTE STRESS AND CHILDHOOD TRAUMATIC EVENTS ON PAIN SENSITIVITY AMONG ADULTS WITH CHRONIC LOW BACK PAIN

by

GABRIELA COMPTDAER

B.A., Boston University, 2020

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2022

Approved by

First Reader _____

Gwynneth D. Offner, Ph.D.
Associate Professor of Medicine

Second Reader _____

Christine B. Sieberg, Ph.D.,Ed.M., M.A.
Assistant Professor of Psychology, Harvard Medical School

ACKNOWLEDGMENTS

Throughout the process of working on this project, I have received a tremendous amount of support and guidance, which I am extremely grateful for. I would firstly like to thank my incredible second-reader and mentor, Dr. Christine Sieberg for her constant support, guidance, and friendship throughout the process of writing this thesis. I would also like to thank Claire Lunde, who has also been a huge mentor and great friend. I am so grateful for my time at the BPP lab, and for everything you both have done and continue to do for me.

Secondly, I would like to thank Dr. Samantha Meints and Dr. Robert Edwards for allowing me join their project and to use their data for this Master's thesis.

I would like to thank my colleagues and great friends, Haley Gagnon and Andrea Wolfson, for their constant support and advice throughout this process. Thank you for making me feel supported and for making my days in the lab filled with laughs.

THE IMPACT OF ACUTE STRESS AND CHILDHOOD TRAUMATIC EVENTS ON PAIN SENSITIVITY AMONG ADULTS WITH CHRONIC LOW BACK PAIN

GABRIELA COMPTDAER

ABSTRACT

Background and aims: Globally**,** chronic low back pain (CLBP) affects 70-80% of adults at some point in their lives and current treatments are widely unsuccessful in relieving pain. Understanding the underlying neurophysiological (e.g., descending pain inhibition) and biobehavioral (e.g., stress) processes contributing to chronic pain in patients with CLBP is needed for the development of novel treatments. Previous studies have shown that acute stress can impact pain sensitivityand that childhood trauma may predispose a person to CLBP, but the mechanisms underlying this impact are unknown. Conditioned Pain Modulation (CPM) is a psychophysical paradigm used in research to assess descending pain modulatory pathways, which are thought to be impaired in patients with CLBP as well as in those with childhood trauma. The overlap of conditions has not been explored. The current study explored the impact of childhood trauma on the CPM response within a sample of patients with CLBP being treated at a tertiary pain clinic. CLBP patients exposed to an acute stress paradigm were expected to shower higher pain sensitivity, with acute stress significantly interacting with a history of childhood trauma as a factor leading to the higher pain sensitivity.

Methods: 46 Participants with CLBP (n=46, mean age=49 years, 55.3% female) recruited from a pain treatment service completed a Quantitative Sensory Testing (QST) and CPM before and after an acute psychological stressor. Participants were randomized to a control (n=25) or an acute-stress (n=21) condition. The acute-stress condition included the Stroop Color Word Task (SCWT) and a mental arithmetic task prior to completing the QST protocol a second time. The control participants did not undergo any additional stressors and completed the QST protocol a second time after a 20-minute break. Participants' CPM response was measured by the average change in pressure pain threshold (PPT) from baseline to the conditioning stimulus (non-dominant hand in ice-water bath). A "Good CPM response" was defined as a CPM effect above 100, indicating that the pain threshold increased when exposed to the conditioning stimulus. To examine the impact of childhood trauma on pain sensitivity, participants completed a Childhood Traumatic Events Scale (CTES) to assess the presence and severity of six types of trauma (death, parental upheaval, sexual, violence, illness or injury, other upheaval) during childhood. The CTES was scored as a continuous variable by calculating the sum the trauma severity for all six trauma types.

Results: A large majority of the sample (94% of participants) showed an increase in pain threshold during hand immersion in ice water, which was contrary to our hypothesis based on prior research done on other chronic pain conditions and CLBP. Participants exposed to an acute stressor had an impaired CPM effect

compared to those that were not exposed to an acute stressor, however there was no difference between groups (p=0.277). A history of childhood traumatic events did not correlate significantly with an impaired baseline CPM or a change in CPM effect when exposed to an acute stressor.

Conclusion: The current study used novel QST modalities, including CPM, to analyze the interaction between acute and chronic stress on pain sensitivity. Ultimately, this study found that exposure to an acute stressor had a negative effect on CPM, indicating that when under experimental stress participants were more sensitive to pain compared to when they were not under stress, although the findings were not statistically significant. These findings should be further investigated to expand the understanding of the neurophysiological mechanisms underlying CLBP and to potentially provide novel treatment modalities for patients with CLBP.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

BWH	Brigham and Women's Hospital
CNS	Central Nervous System
CPM	Conditioned Pain Modulation
CS	Central Sensitization
CTES	Childhood Traumatic Events Scale
DFNS	German Research Network on Neuropathic Pain
DNIC	Diffuse Noxious Inhibitory Controls
fMRI	Functional Magnetic Resonance Imaging
IBS	Irritable Bowel Syndrome
PCS	Pain Catastrophizing Scale
PPT	Pressure Pain Threshold
QST	Quantitative Sensory Testing
RTES	Recent Traumatic Events Scale
SCWT	Stroop Color and Word Test
TMD	Temporomandibular Disorder

INTRODUCTION

Chronic Low Back Pain Definition and Existing Treatments

Chronic low back pain (CLBP) is a highly prevalent condition in the U.S. and affects 70-80% of adults globally at some point in their lives (Becker et al., 2010). CLBP is one of the leading causes of high healthcare costs in the industrialized world, and patients who suffer from chronic pain are often prescribed treatments that are not individualized or evidence-based (Becker et al., 2010), and which often fail to ameliorate symptoms. There is evidence that individuals suffering from lower back pain who do not seek medical treatment, do not differ significantly in terms of pain intensity, compared to those who do seek treatment (Vingård et al., 2002).

The current treatment regimens include use of non-steroidal anti-inflammatory medication (NSAIDs), opioids, physical therapy, spinal manipulation, acupuncture, yoga, or other exercise-based therapy programs. The use of NSAIDs are the most commonly used single class of medications for CLBP, and although effective in alleviating pain, NSAIDs harbor the potential for common gastrointestinal and cardiovascular side effects (Patrick et al., 2014). Long-term opioid use appears to be safe for treatment of CLBP, however, research has shown that there is only modest improvement in both function and pain in these patients, and with long-term medication use these patients are at risk for central nervous system (CNS) depression and development of tolerance. Alternative therapies such as

acupuncture, lack conclusive scientific evidence supporting their efficacy in the treatment of CLBP (Furlan et al., 2005), and therefore cannot be accurately evaluated. Despite this, there is evidence that patients who pursue these alternative therapy options experience symptom relief, at least to some extent (Patrick et al., 2014). With limited options for CLBP treatment, and despite many advances in medicine, clinician's ability to diagnose and treat CLBP remains a challenge.

The etiology in most cases (up to 85%) of CLBP is unknown or nonspecific (Vingård et al., 2002), and CLBP is often multifactorial, and therefore treatment options are currently poor. Moreover, there is a lack of consideration for the CNS involvement in current CLBP treatment. The emerging recognition of the neurophysiological processes underlying CLBP, however, is leading to new and hopefully better treatments.

Neurophysiological Processes Underlying CLBP

Central Sensitization (CS) has recently been recognized as a potential pathophysiological mechanism underlying several chronic pain disorders, including CLBP (Sanzarello et al., 2016), and it provides physicians with a disease framework that patients can understand. CS has been defined as an amplification of the neural signaling within the CNS that elicits pain hypersensitivity, and CS pain results from the dysfunction of neurophysiological processes that occur in one or more

components of the CNS. The current understanding of CS is that prolonged nociceptive input leads to alteration of the morphology of anterograde projection areas in the CNS, which causes them to become hyper alert when there is high risk of further damage. So essentially, pain becomes the result of neuronal changes in the CNS, rather than being elicited by the presence of real noxious stimuli on peripheral nociceptors.

There are several studies that show evidence of CS in patients with CLBP. Giesecke et al., specifically, conducted a study with fMRI to investigate hypersensitivity in idiopathic CLBP patients (Giesecke et al., 2004). This study revealed altered central pain processing by showing evidence that CLBP patients experienced significantly more pain at equal levels or pressure compared to healthy controls, and showed that the CLBP patients had more extensive activation in pain-related cortical areas in functional magnetic resonance imaging (fMRI) (Giesecke et al., 2004). Moreover, patients with CLBP have also been shown to experience generalized deep-tissue hyperalgesia when exposed to mechanical pressure (O'Neill et al., 2007), experiencing decreased pressure pain threshold, higher pain response, and longer duration of pain following saline injections. Several researchers have evaluated different methods of assessment of CS and its influence on patients with chronic pain, and have found that the sensitivity to noxious stimuli can be assessed with quantitative sensory testing (QST) (La Touche et al., 2018). QST is a technique that allows researchers to test a variety of standardized stimuli such as thermal,

mechanical, electrical, and ischemic pain. QST also allows researchers to predict the propensity to develop chronic pain, differential sensitivity to treatment effects, and potential underlying mechanisms of chronic neuropathic pain at the individual level (Treede, 2019). The protocol developed by the German Research Network on Neuropathic Pain (DFNS) includes measures of thermal and mechanical detection threshold, thermal and mechanical pain thresholds, and conditioned pain modulation (CPM), which assesses dynamic modulation of pain sensitivity and can aid in determining the presence of CS.

The majority of pain research during the last decade has focused on static pain parameters of maximum pain tolerance or pain detection threshold; however, the science, has recently shifted to focus on dynamic parameters (Yarnitsky, 2010) that better depict a patient's pain modulation system. Diffuse noxious inhibitory controls (DNIC) emerged as a method to assess the endogenous pain pathway, as recordings from dorsal horn neurons are not feasible in human subjects. DNIC is a dynamic test paradigm, designed to measure the descending pathways, which can be both facilitatory and inhibitory. CPM is the modern term used to describe psychophysical paradigms in which a conditioning stimulus is used to effect a test stimulus, describing the net effect of the endogenous pathways that enhance or diminish the effects of afferent noxious stimuli (Ramaswamy & Wodehouse, 2021). Impaired descending pain modulatory pathways are thought to contribute to the development of central sensitization, and therefore are implicated in chronic pain

conditions. Therefore, CPM has been used in clinical settings to assess pain modulation in patients that suffer from chronic pain conditions.

In recent literature, CPM has been found to be less efficient in patients suffering from chronic idiopathic pain syndromes, such as irritable bowel syndrome (IBS) (Heymen et al., 2010), and temporomandibular disorder (TMD) (King et al., 2009). The literature on CPM deficiency in patients with CLBP however, is mixed and inconclusive. Neelapala et al. (2019) conducted a systematic review of the literature on CPM in CLBP and found that strong conclusions on whether descending pain inhibition is dysfunctional in CLBP could not be reached. Out of the seven studies included in the review, three studies reported significant differences in CPM between patients with CLBP and healthy controls, while four other studies identified no significant differences. Another study conducted by Gerhardt et al. (2017) analyzed CPM in patients with nonspecific CLBP and aimed to compare CPM in patients with different pain extents, either chronic local back pain or chronic widespread back pain. This study indicates that CPM was much higher in chronic local back pain than in patients with chronic widespread backpain, and was even significantly higher than in patients with fibromyalgia, a condition in which CPM has been well documented (Gerhardt et al., 2017). From the literature, it is clear that effects on CPM in patients with CLBP are dependent on several factors, and have been shown to be more individualized than in other chronic pain conditions, and

therefore needs more investigation to fully understand the underlying pain mechanism.

Biobehavioral Mechanisms that Contribute to CLBP

Individual differences in pain sensitivity and reactivity have been attributed to genetic and environmental differences, however, the bases of these individual differences are not entirely understood. The neurophysiological mechanisms that regulate pain perception have been shown to be influenced by the acute stress response (Vachon-Presseau et al., 2013), as seen by individual reactive cortisol response to noxious thermal stimuli. According to Vachon-Presseau et al., individuals with higher reactive cortisol responses experienced increased stress-induced analgesia by engaging their pain-related inhibitory processes which reduced activity in certain brain regions. Studies on animals have shown that experimentally-induced acute stress has an analgesic effect (Bodnar et al., 1980; Butler & Finn, 2009); however, chronic exposure to these stressors results in adaptation of the analgesic response. Furthermore, it has also been noted that exposure to acute psychological stress induces hyperalgesia, not analgesia, in animals (Jørum, 1988; Rivat et al., 2007).

Although these animal studies suggest that there may be a hyperalgesic response to acute psychological stressors, the data on the human response is inconclusive. Crettaz et al. (2013) conducted a study including 10 female healthy subjects and 13

female patients with fibromyalgia and found that both groups showed stress-induced enhancement of pain sensitivity in response to thermal stimuli, but only fibromyalgia patients showed increased sensitivity in response to pressure pain. This study was intriguing, as they found evidence for differential underlying mechanisms determining response to stressors in healthy subjects compared to patients suffering from chronic pain. Geva et al. (2014) conducted a study including several different pain measurements, including CPM to examine the effect of acute stress on pain perception in healthy men. They concluded that acute psychosocial stress does not affect pain sensitivity (Geva et al., 2014). Interestingly, though, they also found that there is a correlation between the magnitude of perceived stress and CPM deficiency, which points towards a dose-response relation between the magnitude of stress and pain modulation.

As the literature has shown that acute stress has a potential effect on pain processing, the relationship between chronic stress and pain sensitivity must also be explored. There is currently limited evidence for the effect of psychosocial factors on patients with CLBP, and the studies that have been done are limited. Schofferman et al., investigated the effect of childhood psychological trauma; defined as sexual abuse, physical abuse, emotional neglect, abandonment, and a chemically dependent caregiver, on chronic refractory low-back pain, and found that multiple childhood traumas may predispose a person to chronic low back pain. Through a retrospective chart review, Schofferman et al. found a strong correlation between three or more

childhood psychological traumas and chronic refractory low-back pain; however, they were not able to state a cause and effect relationship. Another prospective cohort study, done in Canada, found that the risk of back pain was significantly higher for people who experienced two or more childhood traumas, compared to having experienced one (Kopec & Sayre, 2005). Kascakova et al. investigated the effect of childhood trauma on the development of anxiety and pain conditions in the Czech Republic, and similar to Kopec and Sayre, found that adults who experienced more trauma in childhood are at higher risk for developing anxiety with concurrent pain conditions in adulthood (Kascakova et al., 2020). Interestingly, another group of researchers conducted a systematic review and meta-analysis on the interplay between psychological trauma and functional somatic syndrome, including fibromyalgia, chronic widespread pain, temporomandibular disorder (TMD), and irritable bowel syndrome (IBS). This meta-analysis found that individuals who reported exposure to trauma, were 2.7 times more likely to have a functional somatic syndrome, compared to those who reported no trauma history (Afari et al., 2014). Afari et al. do however, highlight the limitations of existing literature and emphasize the important of conducting hypothesis-driven studies of the mechanisms underlying the link between trauma and functional somatic syndromes, of which CLBP is a part.

SPECIFIC AIMS

Although the relationship between acute and chronic psychosocial stress and pain perception has been previously explored, the results have been mixed, and therefore more investigation is necessary. Moreover, a study that investigates the effect of both acute and chronic stress of pain sensitivity, through measurement of CPM, is novel and would significantly add to the current understanding of the underlying mechanism of pain in patients with CLBP. This current study aims to examine the impact of acute stress on pain sensitivity in a sample of patients with CLBP and to assess how a history of childhood trauma may impact this relationship.

To further explore these factors, this current study aims to:

1. Describe the prevalence and type of traumatic childhood events endorsed by participants.
    a. Hypothesis 1: It was hypothesized that the majority of participants will have experienced some sort of trauma, measured by the CTES.
2. Analyze the baseline CPM effect to investigate how CLBP affects pain sensitivity
    a. Hypothesis 2: It was hypothesized that the population investigated in this study; those with CLBP, would have impaired CPM, seen by a CPM effect below 100.
3. Investigate the impact of trauma history on pain sensitivity, measured through baseline CPM.

   a. Hypothesis 3: It was hypothesized that CLBP patients who experienced more childhood and recent traumatic events will endorse greater pain sensitivity at baseline, as seen by impaired CPM.

4. Investigate the impact of exposure to experimental acute stressors on pain sensitivity, measured through change in CPM between baseline and post-stressors.
   a. Hypothesis 4: It was hypothesized that CLBP patients exposed to an experimental acute stress paradigm will endorse greater pain sensitivity compared to those who are not exposed to the acute experimental stressor.
5. Investigate whether a history of childhood traumatic events significantly interacts with the effect of an acute experimental stressor on CPM.
   a. Hypothesis 5: It was hypothesized that acute stress will significantly interact with a history of childhood traumatic events to result in greater pain sensitivity, as seen by impaired CPM effect.

METHODS

Participant Selection and Recruitment

Potential participants were recruited from the Partner's Healthcare Clinical Trials website, where participants were provided study information, eligibility criteria, and compensation information. Eligible participants expressed interest for participation through the Partner's Healthcare Clinical Trials website, where they provided their name and contact information. Participants were also recruited via word of mouth and sharing of the Partner's Healthcare Clinical Trials website on social media (i.e. Facebook, Twitter, and Instagram).

Participants who met the following eligibility criteria were recruited to participate in this study.

- Proficiency in English and the ability to complete questionaries given during the study visit
- Aged 18 to 65 years old
- Self-reported chronic lower back pain (at least 3 months) with an average pain rating of 4 on a scale from 0-10.
- No co-morbid medical and/or pain conditions (e.g. cancer, sickle-cell disease, fibromyalgia, pregnancy)

Once participants expressed interest in involvement, study personnel contacted potential participants via a phone call or email to confirm eligibility and schedule the study visit.

Study Visit Procedure Overview

Upon arrival to the laboratory, participants were escorted to a private room where they reviewed all consent procedures with study personnel. Once consent was obtained, participants underwent a baseline QST battery, described below, before completing a series of questionnaires on their emotional state at four different time points throughout the protocol. After completion of baseline QST and questionnaires, participants were randomly assigned to two groups:

1. *High-Stress Group* – Completed the Stroop Test and Mental Arithmetic Task, explained below, before continuing to undergo the QST battery.
2. *Control Group* – The control group was not exposed to any acute stressors. Instead, they had a 20 minute waiting period prior to repeating the QST protocol.

At the end of the study, all participants were debriefed and received compensation for their time and effort.

Adjective Ratings

Participants were asked to rate their emotional state at four different time points throughout the study protocol. They were asked to rate each emotion, out of a list of four different emotions, on a scale from 0 – 10. (0 = Not at all, 10 = Extremely). The emotions participants were asked to rate were the following:

1. Stress
2. Calmness

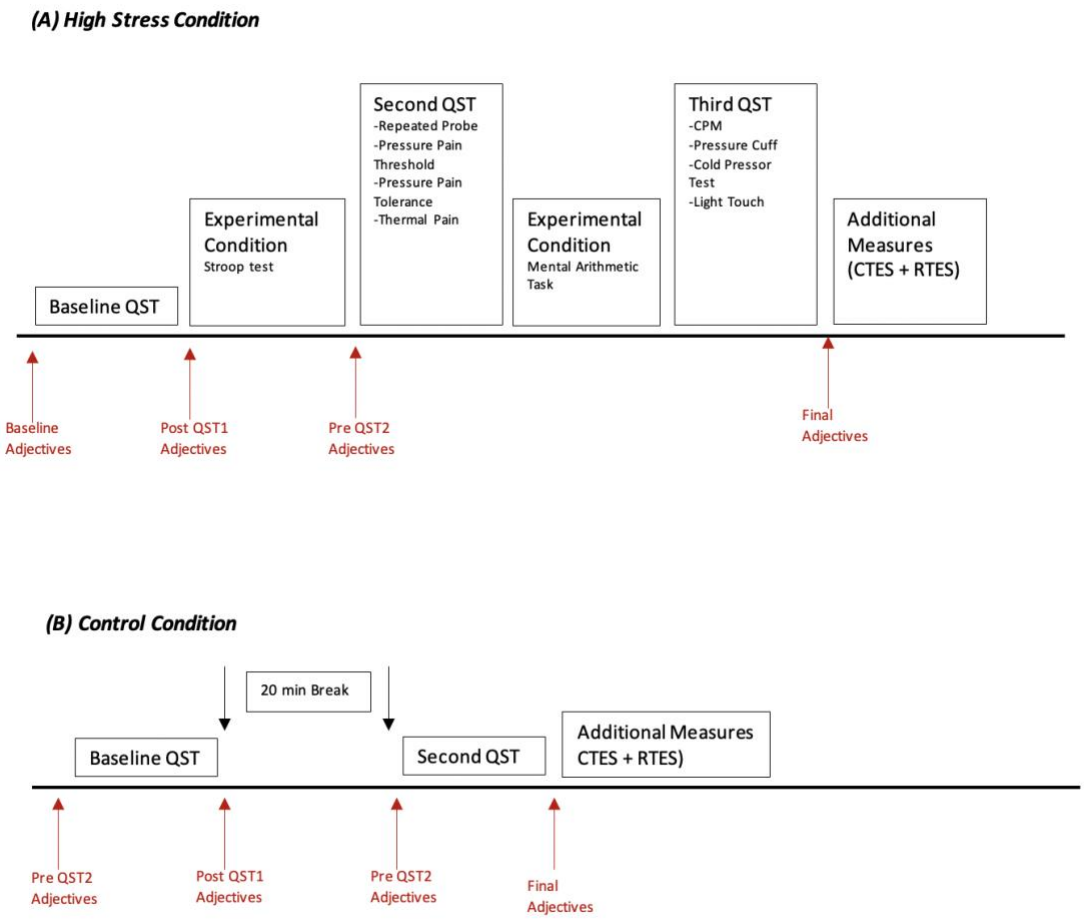

Figure 1. ***Overview of Research Study Protocol***

This figure outlines an overview of the research study visit, including all rounds of QST and questionnaires given to participants during the study visit. (A) The protocol that the High Stress Condition participants underwent. (B) The protocol that the control participants (no acute stressor) underwent.

Baseline QST Procedure

The QST protocol followed in this study was based off of the comprehensive standardized protocol developed by the German Research Network on Neuropathic Pain (DFNS) (Rolke et al., 2006). This QST protocol was developed as a battery of

tests to quantify functioning of individual's somatosensory nervous system. In the baseline QST protocol followed in this study, participants underwent the following battery:

(1) Light Touch Detection

The light touch test is a simple way of screening for sensation abnormalities. For this task, A von Frey monofilament kit, consisting of monofilaments of increased diameter, was used. The monofilaments expert a constant force as the monofilament bends, and participants were asked to endorse whether or not they felt the monofilament. The light touch detection threshold was defined as the minimum monofilament diameter that resulted in sensation.

(2) Pressure Pain Sensation

Pressure algometry is the most commonly used for static mechanical pressure sensation in clinical research. In this protocol, an electronic pressure algometer was used to deliver firm and quantifiable pressure on participants' thumb joint and trapezius. The algometer was used to apply increasing pressure to the test site, until a maximum pain threshold was reached. Participants were asked to tell study personnel when they could no longer tolerate the pain, and the pressure and pain rating (on a scale of 0-100) at that point in time was recorded.

(3) Temporal Summation (Wind-Up Pain Perception)

Temporal summation, also referred to as wind-up pain perception, is used as an index of central pain-faciliatory processes. For this test, punctate mechanical stimulation was applied to the participants' finger at a frequency of 1Hz. Ten stimuli were applied at the same site, and participants were asked to rate the pain sensation from the first, fifth, and tenth stimuli. The wind-up phenomenon occurs with progressive increased pain with repeated stimulation, and can serve as an index for central sensitization.

(4) Thermal Quantitative Sensory Testing

Thermal pain responses are commonly used methods of pain induction in the laboratory, and were used in the baseline QST battery of this protocol. Heat pain responses were assessed using a contact thermode that delivered contact heat, using a computer-controlled system (Medoc). The contact thermode was positioned on the skin of the forearm, and delivered gradually increasing heat. Participants were asked to push a button as soon as the sensation became painful, which caused the temperature to stop increasing, and the thermode returned to a baseline temperature of 32°C. This maximum temperature was recorded as the "heat pain threshold".

Cold pain responses were assessed using the cold pressor task (CPT), which involves the immersion of the dominant hand in a circulating water bath maintained

at a temperature of 4°C. Participants were asked to leave their hand immersed in the cold water until they could no longer tolerate the pain, or a maximum of three minutes. During this time, study personal asked participants to provide a pain rating from 0-100 at fifteen second intervals.

(5) Conditioned Pain Modulation (CPM)

CPM refers to the phenomenon of one noxious stimulus inhibiting the pain perception of a second noxious stimulus. To assess CPM in this protocol, pressure pain threshold (PPT) was first assessed at the trapezius using the pressure algometer. To assess PPT, study personnel used an electronic pressure algometer that delivered constant quantifiable pressure. The participant was asked to push a button that ended the test when the sensation became painful. The specified pressure was recorded as the participant's baseline PPT.

Once the baseline PPT was found, participants underwent two brief cold pressor tasks where they were asked to immerse their hand in circulating cold water (4°C) for sixty seconds, or until the pain become intolerable. Fifteen seconds after the hand was first immersed in the water bath, PPT was assessed at the trapezius again while the participant's hand remained in the cold water. Participants underwent two trials to assess their CPM.

The CPM effect is defined as the average change in PPT from baseline while the participant is also experiencing a noxious cold stimulus from the water bath. For this study, CPM was calculated as the percent difference in PPT between the baseline PPT measurement and the threshold found while the participant's hand was in the water bath, using the following formula:

$$CPM = \frac{PPT\ on\ trapezius\ during\ cold\ water\ immersion}{PPT\ on\ trapezius\ at\ baseline} * 100\%$$

CPM values above 100 are considered "good CPM", indicating that the pain threshold increased when exposed to the conditioning stimulus: the cold water bath, and the higher the values of CPM, the better.

Acute Psychosocial Stressors

Once participants completed the baseline QST battery, they were exposed to the following acute stressors:

(1) The Stroop Color and Word Test (SCWT) (Stroop, 1936)
The SCWT is a neuropsychological test that assesses the ability to inhibit cognitive interference, which occurs when the processing of one stimulus features interferes with the processing of another feature. SCWT requires participants to read three different tables as quickly as possible, two of which represent the "congruous condition" in which participants read names of colors printed in black ink and name

different color patches. In the third table, the “incongruent condition”, color words are printed in inconsistent ink and participants were asked to name the color of the ink instead of reading the word. For example, the word “green” is printed in red ink, and participants must verbally respond “red” in this task.

In the incongruent condition, participants must perform a less automated task (naming the ink color) while inhibiting the interference from a more automated task (reading the word), and the difficulty in inhibiting the more automated process is called the “Stroop effect” (Scarpina & Tagini, 2017). Heart rate has been shown to increase throughout the Stroop Test, which indicates that it could be an effective simulated stressors (Renaud & Blondin, 1997), and was therefore used in as a stressor in the high-Stress condition of our experimental protocol. Once the SCWT was completed, participants continued onto the second block of QST.

(2) Mental Arithmetic Task

The mental arithmetic task performed in the high-stress experimental condition of the protocol was shown to increase heartrate and serve as an effective laboratory stressor (Liao & Carey, 2015). This task required participants to count backwards by 7’s from 978 as fast as they could, without errors. Once the mental arithmetic task was completed, participants continued onto the third block of QST.

QST Performed After Exposure to Acute Stressors

The entire QST battery was repeated after exposure to acute stressors, however the battery was split up into two parts: one directly after the SCWT, and one after the mental arithmetic task, as outlined in Figure 1. The following analysis focused solely on CPM, as described above, because as stated previously, CPM is a good clinical method of analyzing central sensitization and can shed light on differences in dynamic pain responses.

Measures Completed After Experimental Condition and Second QST

(1) Childhood and Recent Traumatic Events Scales (CTES and RTES) (Pennebaker & Susman, 1988)

The Childhood Traumatic Events Scale (CTES) is commonly used to assess the presence and individual impact of childhood trauma. The questionnaire measures 6 stressful early life events that occurred prior to the age of 17, including death of a family member or close friend, parental divorce, traumatic sexual experiences (e.g. rape, sexual assault), traumatic violent experiences (e.g. child abuse, assault), history of serious, or other events that could have disrupted a child's early life. The Recent Traumatic Events Scale (RTES) is similar to CTES, however it measures 7 possibly traumatic events that occurred in the past 3 years. RTES measures separation/divorce from a spouse or significant other instead of parental separation, and adds in a new measure of job changes. While participants completed

this measure, the current project mainly focused on traumatic events that occurred during childhood.

CTES and RTES asks participants to report whether or not they experienced certain types of trauma and asks them to rate the severity of each of those traumas they endorsed on a scale of 0-7 (0 = no exposure, 1 = not at all traumatic, 4 = somewhat traumatic, 7 = extremely traumatic). Additionally, participants are asked to endorse whether or not they confided in other people after the event occurred, on a scale of 0-7 (7 = a great deal).

The CTES and RTES questionnaires were administered after the experimental condition and final QST measure in order to prevent bringing up potentially stressful childhood memories that could interfere with the sensory testing.

Data Analysis

All of the following analyses were carried out using IBM SPSS version 27.0.1. The data set was deidentified and only accessible to approved study personnel. Descriptive statistics were run to characterize the sample based on age, gender, ethnicity, and race, and independent measures t-tests were run to ensure there were no statistically significant differences in participants in the different stress conditions. The Kolmogorov-Smirnov test was also run to test assumptions of

normality in order to proceed with the following statistical analyses to examine the effect of acute stressors and a history of childhood trauma on CPM.

For the purposes of this analysis, the CTES questionnaire was scored in various ways. Participants were grouped into those that reported any number greater than 1 childhood traumatic event (Trauma group) and those that did not report any childhood traumatic events (No Trauma). Participants in the trauma group were further separated into a more specific trauma group (Violent Trauma), that included participants that experienced violent traumas; defined as sexual or violent physical trauma in childhood and participants that did not experience violent traumas but were grouped into the No Violent Trauma group.

Continuous scoring variables were created for the CTES assessment, in which the sum of trauma severity scores across all 6 stressful early life events (CTES) and 6 recent life events (RTES) was calculated. Higher scores indicated higher self-reported trauma experience. Additionally, another continuous scoring variable was created to assess the total number of violent traumas experienced in the 6 early life events.

Independent samples t-tests were conducted to assess variance in baseline CPM scores between groups (i.e. Violent Trauma and No Violent Trauma groups), and independent samples t-tests were also used to compare other categorical and

continuous variables within the study, utilizing a 95% confidence interval each time. A Pearson's Correlation was also conducted to assess the continuous variables created for CTES to assess the impact the number of traumas could have on baseline CPM. Additionally, a mixed repeated-measures ANOVA (Analysis of Variance) was conducted to investigate the impact of an acute stressor on the CPM effect for each participant. Finally, the impact of trauma history on change in CPM effect after acute stressor exposure was investigated by finding the change in CPM effect and then using a Pearson's correlation.

RESULTS

Prior to proceeding with the following statistical analyses, the 2 groups (Stress vs. No Stress) were tested for the assumption of normality using the Kolmogorov-Smirnov test. There was no statistically significant difference found in either group (No Stress: $D(25) = 0.128$, $p=0.2$, Stress: $D(22) = 0.178$, $p=0.067$), indicating that the assumption that the groups follow a normal distribution can be followed.

Participant Demographics

Of the total number of participants that were contacted for this study, 54 participants with CLBP came in and participated in the complete battery of QST and responded to the CTES questionnaires. The participant's ages ranged from 22-64, with a mean age of 49 years old (SD=14.71) for the entire sample. The self-identified gender frequency was explored, and the majority of the sample identified as female (55.3%). The majority of participants in the study identified as not Hispanic or Latino (91.5%), however, there was some diversity with 6.4% of participants identifying as being Hispanic or Latino. Our study sample did however, have an inclusive distribution of self-reported race when compared to the racial distribution in the entire population of the US reported by the US Censes, as seen in Figure 2.

Table 1 describes the demographic characteristics analyzed above, separated by the stress condition grouping variable used for all further analyses. As seen in Table 1, the mean age of the No Stress group was 50.4, whereas the mean age of the Stress

group was 46.3. When a t-test was conducted to compare the ages between the two groups, there was no significant difference, indicating that there is no significant difference in mean age between the two groups.

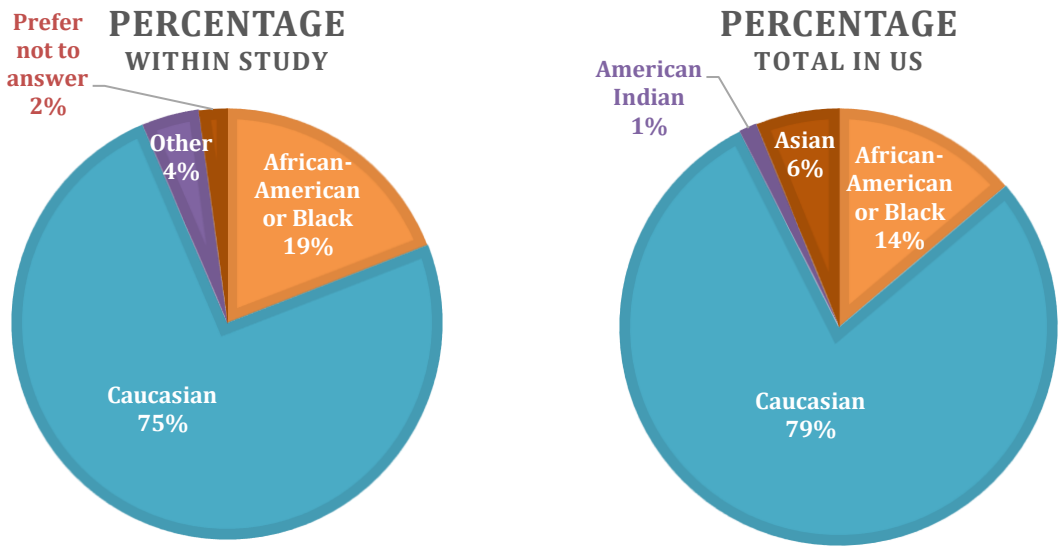

Figure 2. ***Distribution of Race in the Study Sample Compared to the Total US Population***

Table 1. ***Demographic Characteristics of Chronic Lower Back Pain Participants***

Baseline Characteristics	No Stress Condition		Stress Condition		Entire Sample	
	n	*%*	*n*	*%*	*n*	*%*
Self-Identified Gender						
Female	13	*52*	13	*59.1*	26	55.3
Male	12	*48*	*9*	*40.9*	21	44.7
Ethnicity						
Hispanic or Latino	*1*	*4*	2	*9.1*	3	6.4
Not Hispanic or Latino	*23*	92	20	90.9	43	91.5
Prefer not to answer	1	*4*	0	0	1	2.1
Race						
African-American or Black	*3*	12	6	27.3	9	19.1
Caucasian	20	80	15	*68.2*	35	74.5
Other	1	*4*	1	4.5	2	4.3
Prefer not to answer	1	*4*	0	0	1	2.1
Age						
Range	23 – 65		22 - 64		*22 – 65*	
Mean	50.40		46.29		*48.52*	

Participant Trauma History

Aim 1: Describe the prevalence and type of traumatic childhood events endorsed by participants.

Tables 2 and 3 described the trauma history of the cohort of participants in this study, separated by stress condition. As described previously, participants were grouped based on their experience of trauma (both CTES and RTES), and then those participants that experienced trauma were further divided based on their experience with violent trauma; defined as sexual or violent physical trauma. As seen in Table 2, the majority of participants in the no stress condition (88%) endorsed experiencing some type of trauma either in childhood or recently, and all of the participants that completed the CTES/RTES questionnaires endorsed some type of trauma in the stress condition. In both the no stress and stress conditions, 1 participant did not complete the CTES and RTES questionnaires due to their own comfort level. In the no stress condition, 48% of participants endorsed experiencing violent traumas and 48% of participants endorsed experiencing no violent traumas. In the stress condition, only 27.3% of participants endorsed no violent trauma history, and 68.2% of participants endorsed experiencing violent trauma. When an independent t-test was run, however, there was no statistically significant difference found in the trauma history between the no stress and stress condition groups.

Table 3 outlines the range, mean, and standard deviation of the traumas endorsed in the CTES and RTES questionnaires. There were no statistically significant differences found in trauma history between the stress and no stress groups, when an independent t-test was run for each variable.

Table 2. ***Trauma Grouping Based on CTES and RTES Scores***

	No Stress Condition		Stress Condition	
	n	*%*	*n*	*%*
Trauma Group				
No Trauma	2	8	0	0
Trauma	22	88	21	95.5
Missing	1	4	1	4.5
Violent Trauma				
No	12	48	6	27.3
Yes	12	48	15	68.2
Missing	1	4	1	4.5

Table 3. ***Childhood and Recent Traumatic History for Chronic Lower Back Pain Participants***

	No Stress Condition			Stress Condition		
	Range	Mean	STD	Range	Mean	STD
Total CTES Trauma Score (0-42)	4 - 33	16.84	9.11	4 - 33	13.75	8.14
Total RTES Trauma Score (0-42)	4 - 32	12.84	7.78	3 - 35	13.05	8.67
Total Number of Traumas (0-12)	0 - 9	4.21	2.78	1 - 9	4.71	2.26
Total Number of Violent Traumas (0-4)	0 - 3	0.83	1.05	0 - 3	1.14	0.96

Participant Baseline CPM Effect

Aim 2: Analyze the baseline CPM effect, to see how CLBP affect pain sensitivity

Participants in the population of this experiment were all patients with CLBP, with varying degrees of functional disability. Their baseline CPM was assessed prior to exposure to any experimental stressors, and the mean CPM effect at baseline was found to be 141.60 (Min = 69.58, Max=251.28, SD=36.49). There were only 3 participants that had a baseline CPM below 100 (and below 130) in the population tested.

Table 4. ***Frequency of Participants with Good Baseline CPM***

	Baseline CPM Above 100		Baseline CPM Above 130	
	n	%	n	%
No	3	6.7	3	6.7
Yes	44	93.6	44	93.6

How Trauma History Affects Pain Sensitivity at Baseline

Aim 3: Investigate the impact of violent and non-violent trauma history on pain sensitivity, measured through baseline CPM.

To investigate the first aim of this study, baseline CPM in the participants prior to exposure to experimental acute stressors was analyzed, as seen in tables 4 and 5, using the categorical variables created for trauma groups. There was no statistically significant difference in the CPM effect between participants who endorsed trauma vs. those that endorsed no trauma ($t(43) = 1.11$, $p = 0.273$), although the participants in the trauma group had a higher mean average CPM at baseline ($M=144.19$, $SD=37.04$) compared to those in the no trauma group ($M= 114.75$, $SD=12.58$). Then, participants who endorsed experiencing violent trauma vs. non-violent traumas were analyzed as well. Similarly, there was no statistically significant difference in baseline CPM between participants that experienced violent trauma compared to those that did not ($t(43) = 0.77$, $p = 0.488$).

Table 5. ***Baseline CPM Effect in Participants Split by Trauma Group***

	No Trauma Group				Trauma Group			
	n	*Range*	*Mean*	*STD*	*n*	*Range*	*Mean*	*STD*
Average Baseline CPM Effect	2	105.86 – 123.65	114.75	12.58	43	69.57 – 251.28	144.19	37.04

Table 6. ***Baseline CPM Effect in Participants Split by Violent Trauma Group***

	No Violent Trauma Group				Violent Trauma Group			
	n	*Range*	*Mean*	*STD*	*n*	*Range*	*Mean*	*STD*
Average Baseline CPM Effect	18	105.86 – 189.85	138.15	24.66	27	69.58 – 251.28	146.03	43.15

To analyze childhood traumatic experiences in a different way, the continuous variables of total CTES trauma scores and the total number of violent trauma scores were used as well. When a Pearson's correlation was run to investigate whether childhood traumatic history correlated with baseline CPM, it was found that there was no significant correlation, as reported in Table 6.

Table 7. ***Pearson Correlation for Childhood Trauma History on Baseline CPM***

	n	Pearson Correlation	Significance (2-tailed)
Sum of traumas (CTES)	45	0.057	0.709
Sum of all trauma severity scores (CTES)	39	-0.114	0.489
Number of violent traumas (CTES)	45	0.042	0.782

How Exposure to Acute Stress Affects Pain Sensitivity

Aim 4: Investigate the impact of exposure to experimental acute stressors and a history of childhood trauma on pain sensitivity, measured through change in CPM between baseline and post-stressors.

To investigate how the CPM effect changes after exposure to an acute experimental stressor, a mixed repeated measures ANOVA (Analysis of Variance) was used. The descriptive statistics are laid out in Table 8, which shows the mean and standard deviation of the CPM % Change during each round of QST.

The mixed repeated measures ANOVA revealed that there was no statistically significant difference found between the stress and no stress conditions ($F(1,1) = 1.215$, $p = 0.277$), although as seen in Table 8 and Figure 3 there was a decrease in mean CPM effect after exposure to an acute experimental stressor (QST1: M=152.46, SD=30.98, QST2: M=143.96, SD=30.80), compared to those in the control condition

(QST1: M=132.95, SD=39.70, QST2: M=131.02, SD=26.31). From Tables 8 and 9 and Figure 3, it can be seen that the mean CPM change is negative, indicating that participants under stress had inefficient pain modulation, and had a higher pain sensitivity when under stress.

Table 8. ***CPM Effect in Participants Split by Stress Condition***

	No Stress Condition			*Stress Condition*		
	n	*Mean*	*STD*	*n*	*Mean*	*STD*
CPM % Change During QST1	*24*	*132.95*	*39.70*	*21*	*152.46*	*30.98*
CPM % Change during QST2		*131.02*	*26.31*		*143.96*	*30.80*

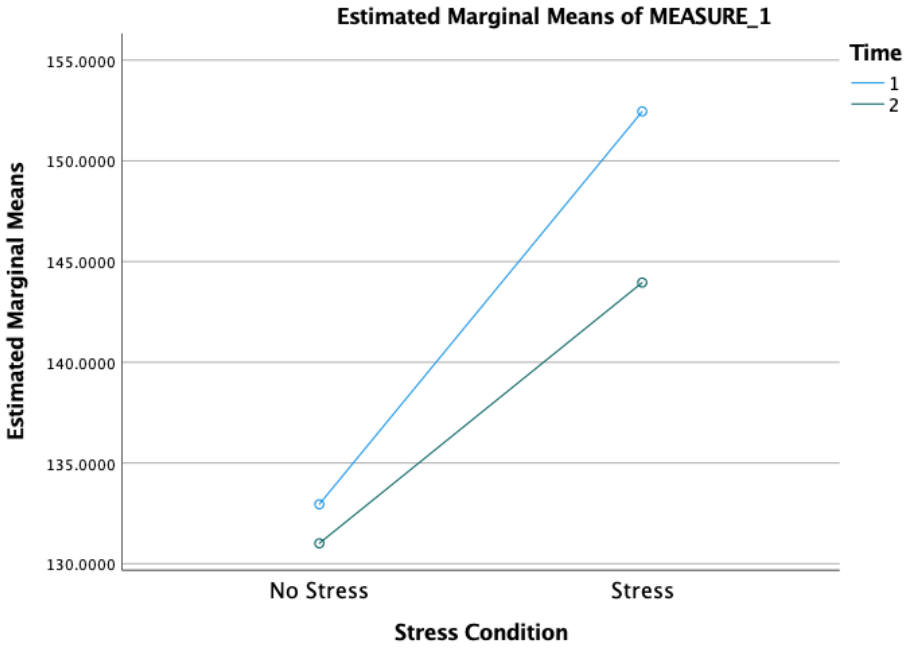

Figure 3. ***CPM Effect during Baseline QST and QST2 in Participants Split by Stress Condition***

How Trauma History Interacts with the Acute Stressor Effect on CPM

Aim 5: Investigate whether a history of childhood traumatic events significantly interacts with the effect of an acute experimental stressor on CPM.

To look at the change in CPM between baseline and after exposure to the acute experimental stressors, a continuous variable called “Absolute CPM Change” was calculated, by taking the difference between the average % change in CPM during

baseline and QST2. The range, mean, and standard deviation for CPM change are reported in Table 8.

Then, to investigate the effect of childhood traumatic experiences on the CPM change, a Pearson correlation was run to investigate whether a history of trauma correlated with the change in CPM observed after acute stressor exposure. To investigate this, we used the continuous variable described above for the total number of traumas experienced (both CTES and RTES). Similarly to above, there was no statistically significant correlation between the trauma experienced and the change in CPM after exposure to the SCWT and mental arithmetic task (No Stress Condition: $r(24)= -0.097$, $p=0.66$, Stress Condition: $r(21)= 0.187$, $p=0.417$).

Table 9. ***CPM Change for Participants Split by Stress Condition***

	No Stress Condition				*Stress Condition*			
	n	*Range*	*Mean*	*STD*	*n*	*Range*	*Mean*	*STD*
Absolute CPM Change	*24*	*-98.37 – 61.42*	*-1.94*	*33.05*	*21*	*-68.65 – 43.59*	*-8.50*	*30.04*

DISCUSSION

This study aimed to add to existing literature and to further the current understanding of the neurophysiological processes contributing to chronic back pain by assessing centralized pain mechanisms in a population of participants suffering from CLBP. It is well understood, though, that individual differences in CLBP can be attributed to genetic and environmental differences, and therefore these biobehavioral factors were also investigated in this study. To investigate the highly individualized experiences of CLBP, this study also aimed to understand the effect of acute and chronic stress on pain sensitivity, by investigating the effect childhood and recent traumatic events on pain modulation.

This particular study focused on the CPM effect in a population of adults with CLBP to investigate the effect of traumatic experiences on the CNS. As seen in previous studies, there was no clear understanding on the affect CLBP had on CPM, and much less understanding on the impact childhood traumatic experiences have on pain sensitivity in people with chronic pain. Although many results were not statistically significant, this pilot study elucidated the need to further investigate the impact of trauma history on CPM in a population of patients with CLBP.

Interestingly, this study revealed that the majority of the population in this cohort (93.6%) do not experience impaired CPM at baseline, although they suffer from CLBP. There are several possible explanations for this observation, the most striking

being that all of the participants were recruited from a pain treatment center, and the treatment they had previously received could have improved their functionality and helped their pain modulation. Another possible explanation, which should be investigated further, is that participants in this cohort could have been highly functional and not as debilitated by CLBP as those in other studies. As this study required participants to come into the lab for sensory testing, it is highly probable that the majority of participants that came in for the study were somewhat functional and were able to care for themselves.

As hypothesized, the investigation on whether exposure to an acute experimental stressor affects pain sensitivity, led to the finding that exposure to an acute stressor had a negative effect on CPM. A negative effect on CPM means that participants were more sensitive to pain and there was less of a descending inhibitory effect when simultaneously exposed to another painful stimuli, compared to baseline. Although this finding was not statistically significant, it is evident from Table 8 and Figure 9 that there was a decrease in CPM effect in participants in the stress condition, which should be explored in a larger sample.

Although there was no statistically significant correlation found for childhood and recent traumatic history affecting baseline CPM, it would be interesting to investigate this further. Schofferman et al., hypothesize that insecure or disrupted early attachment in relationships leaves children with increased psychological

vulnerability to chronic pain, and sexual, physical, and emotional abuse all violate the basic security and comfort the attachment figure must provide. Logically, then more childhood abuse would leave an adult more vulnerable to risk of chronic pain. This effect is not seen in this study, however. It would also be interesting to further investigate trauma history based on type of trauma, similar to how violent and non-violent traumas were investigated in this study. It could also be important to ask participants about their trauma experiences, how they believe the trauma has affected their life, and how they have coped with this trauma, for qualitative analysis. This study did not ask participants whether or not they sought out professional help after violent traumas, and this could be an important factor to consider when assessing the impact of specific childhood traumas on participants in adulthood.

Clinical Implications

As seen in Table 4, the majority (93%) of participants suffering from CLBP in this study did not experience impaired CPM, as was expected based on previous literature on CLBP, fibromyalgia, and other chronic pain conditions. Although this needs to be studied further in a larger patient population, it is important to consider clinically. It is also important to consider that CLBP may have a different pain mechanism compared to other common chronic pain conditions, and therefore the management and treatment of CLBP should also be different in clinical settings.

As stated above, there is an evident effect of acute stressors on pain sensitivity and pain modulation, as seen by impaired CPM after acute experimental stress exposure. This finding could be important to consider clinically, as patients who suffer from chronic pain conditions could benefit from counselling and learning coping skills for stressful life events, especially since living with a chronic pain condition is stressful in itself.

Limitations

Although the study sample was inclusive in terms of race when compared to the racial distribution in the US, the sample size was quite small, especially when split into stress conditions. Additionally, the sample size consists of an older population, with a mean age of 49. Although understandable because this study investigated CLBP, which is more common in the older population, future studies should be mindful of this when comparing to a healthy population. Additionally, in future studies it could be important to control for functional disability when assessing participants with CLBP, as many participants could be relatively functional while others could be relatively disabled and it is important to make a distinction between them.

CTES and RTES measures used in this investigation are helpful tools for childhood and recent traumatic history, however, they are self-report measures and are therefore far from perfect. The possibility that participants choose not to report trauma they experienced remains high, even though the reports are anonymous. Additionally, some memories of adverse events could have been repressed and not reported on CTES or RTES. Self-report measures are also incredibly subjective, and some participants who experienced more severe events could have endorsed some adverse events as not being traumatic, while other participants would have endorsed them as traumatic. While still important, the subjectivity is also what is being analyzed here as how impactful a specific event was to each individual participant is what would affect their pain modulation and not how an average individual would rate each trauma.

When analyzing the adjective ratings of participants before and after exposure to the acute experimental stressors, we noticed that most participants did not rate being any more stressed than at baseline. This is another limitation in the study, as to ultimately induce experimental stress we need to ensure that the tasks are being endorsed as stressful to participant. Again, these adjective ratings were self-report measures and are not perfect as some participants could have not wanted to admit that the SCWT and the mental arithmetic task were causing them stress.

Finally, CPM only measures one pathway of the descending inhibitory system and should be used in conjunction with other measures, such as offset analgesia(Shulman et al., 2020).

Future Directions

This study provided preliminary data that can be analyzed to understand the relationship between acute and chronic stress on pain sensitivity, specifically on CPM. Future studies, however, should include more participants in each stress condition, and should compare participant with CLBP to a population without chronic pain conditions. It would also be interesting to investigate whether previous treatments, separated by type of treatment, and whether the amount of time a participant suffers from the chronic pain condition affects their baseline CPM. Similarly, it would be interesting to investigate other demographic factors that could affect one's response to pain modulation, such as mental health history, gender identity/biological sex, and education level.

CONCLUSION

Ultimately, this study found that exposure to an acute stressor had a negative effect on CPM, indicating that when under experimental stress participants were more sensitive to pain compared to when they were not under stress, although the findings were not statistically significant. Additionally, it was interesting that most participants with CLBP experienced a good CPM response at baseline, and this finding should be investigated further to broaden the understanding of the neurophysiological mechanisms underlying CLBP, as this finding was contrary to our expectations based on prior research. Future research with a greater sample size and a comparison to a population without chronic pain could strengthen these findings and elaborate on the effect of CLBP on pain sensitivity. Further research must also be done to understand the effect of chronic stress, specifically trauma history, on pain modulation as well.

REFERENCES

Afari, N., Ahumada, S. M., Wright, L. J., Mostoufi, S., Golnari, G., Reis, V., & Cuneo, J. G. (2014). Psychological trauma and functional somatic syndromes: A systematic review and meta-analysis. *Psychosomatic Medicine*, *76*(1), 2–11. https://doi.org/10.1097/PSY.0000000000000010

Becker, A., Held, H., Redaelli, M., Strauch, K., Chenot, J. F., Leonhardt, C., Keller, S., Baum, E., Pfingsten, M., Hildebrandt, J., Basler, H.-D., Kochen, M. M., & Donner-Banzhoff, N. (2010). Low back pain in primary care: Costs of care and prediction of future health care utilization. *Spine*, *35*(18), 1714–1720. https://doi.org/10.1097/brs.0b013e3181cd656f

Bodnar, R. J., Kelly, D. D., Brutus, M., & Glusman, M. (1980). Stress-induced analgesia: Neural and hormonal determinants. *Neuroscience and Biobehavioral Reviews*, *4*(1), 87–100. https://doi.org/10.1016/0149-7634(80)90028-7

Butler, R. K., & Finn, D. P. (2009). Stress-induced analgesia. *Progress in Neurobiology*, *88*(3), 184–202. https://doi.org/10.1016/j.pneurobio.2009.04.003

Furlan, A. D., van Tulder, M. W., Cherkin, D. C., Tsukayama, H., Lao, L., Koes, B. W., & Berman, B. M. (2005). Acupuncture and dry-needling for low back pain. *The Cochrane Database of Systematic Reviews*, *1*, CD001351. https://doi.org/10.1002/14651858.CD001351.pub2

Gerhardt, A., Eich, W., Treede, R.-D., & Tesarz, J. (2017). Conditioned pain modulation in patients with nonspecific chronic back pain with chronic local

pain, chronic widespread pain, and fibromyalgia. *Pain*, *158*(3), 430–439. https://doi.org/10.1097/j.pain.0000000000000777

Geva, N., Pruessner, J., & Defrin, R. (2014). Acute psychosocial stress reduces pain modulation capabilities in healthy men. *Pain*, *155*(11), 2418–2425. https://doi.org/10.1016/j.pain.2014.09.023

Giesecke, T., Gracely, R. H., Grant, M. A. B., Nachemson, A., Petzke, F., Williams, D. A., & Clauw, D. J. (2004). Evidence of augmented central pain processing in idiopathic chronic low back pain. *Arthritis and Rheumatism*, *50*(2), 613–623. https://doi.org/10.1002/art.20063

Heymen, S., Maixner, W., Whitehead, W. E., Klatzkin, R. R., Mechlin, B., & Light, K. C. (2010). Central processing of noxious somatic stimuli in patients with irritable bowel syndrome compared with healthy controls. *The Clinical Journal of Pain*, *26*(2), 104–109. https://doi.org/10.1097/AJP.0b013e3181bff800

Jørum, E. (1988). Analgesia or hyperalgesia following stress correlates with emotional behavior in rats. *Pain*, *32*(3), 341–348. https://doi.org/10.1016/0304-3959(88)90046-2

Kascakova, N., Furstova, J., Hasto, J., Madarasova Geckova, A., & Tavel, P. (2020). The Unholy Trinity: Childhood Trauma, Adulthood Anxiety, and Long-Term Pain. *International Journal of Environmental Research and Public Health*, *17*(2), E414. https://doi.org/10.3390/ijerph17020414

King, C. D., Wong, F., Currie, T., Mauderli, A. P., Fillingim, R. B., & Riley, J. L. (2009). Deficiency in endogenous modulation of prolonged heat pain in patients with Irritable Bowel Syndrome and Temporomandibular Disorder. *Pain*, *143*(3), 172–178. https://doi.org/10.1016/j.pain.2008.12.027

Kopec, J. A., & Sayre, E. C. (2005). Stressful experiences in childhood and chronic back pain in the general population. *The Clinical Journal of Pain*, *21*(6), 478–483. https://doi.org/10.1097/01.ajp.0000139909.97211.e1

La Touche, R., Paris-Alemany, A., Hidalgo-Pérez, A., López-de-Uralde-Villanueva, I., Angulo-Diaz-Parreño, S., & Muñoz-García, D. (2018). Evidence for Central Sensitization in Patients with Temporomandibular Disorders: A Systematic Review and Meta-analysis of Observational Studies. *Pain Practice: The Official Journal of World Institute of Pain*, *18*(3), 388–409. https://doi.org/10.1111/papr.12604

Liao, L.-M., & Carey, M. G. (2015). Laboratory-induced Mental Stress, Cardiovascular Response, and Psychological Characteristics. *Reviews in Cardiovascular Medicine*, *16*(1), 28–35.

O'Neill, S., Manniche, C., Graven-Nielsen, T., & Arendt-Nielsen, L. (2007). Generalized deep-tissue hyperalgesia in patients with chronic low-back pain. *European Journal of Pain (London, England)*, *11*(4), 415–420. https://doi.org/10.1016/j.ejpain.2006.05.009

Patrick, N., Emanski, E., & Knaub, M. A. (2014). Acute and chronic low back pain. *The Medical Clinics of North America*, *98*(4), 777–789, xii. https://doi.org/10.1016/j.mcna.2014.03.005

Pennebaker, J. W., & Susman, J. R. (1988). Disclosure of traumas and psychosomatic processes. *Social Science & Medicine (1982)*, *26*(3), 327–332. https://doi.org/10.1016/0277-9536(88)90397-8

Ramaswamy, S., & Wodehouse, T. (2021). Conditioned pain modulation-A comprehensive review. *Neurophysiologie Clinique = Clinical Neurophysiology*, *51*(3), 197–208. https://doi.org/10.1016/j.neucli.2020.11.002

Renaud, P., & Blondin, J. P. (1997). The stress of Stroop performance: Physiological and emotional responses to color-word interference, task pacing, and pacing speed. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology*, *27*(2), 87–97. https://doi.org/10.1016/s0167-8760(97)00049-4

Rivat, C., Laboureyras, E., Laulin, J.-P., Le Roy, C., Richebé, P., & Simonnet, G. (2007). Non-nociceptive environmental stress induces hyperalgesia, not analgesia, in pain and opioid-experienced rats. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *32*(10), 2217–2228. https://doi.org/10.1038/sj.npp.1301340

Rolke, R., Baron, R., Maier, C., Tölle, T. R., Treede, -D. R., Beyer, A., Binder, A., Birbaumer, N., Birklein, F., Bötefür, I. C., Braune, S., Flor, H., Huge, V., Klug, R., Landwehrmeyer, G. B., Magerl, W., Maihöfner, C., Rolko, C., Schaub, C., …

Wasserka, B. (2006). Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. *Pain*, *123*(3), 231–243. https://doi.org/10.1016/j.pain.2006.01.041

Sanzarello, I., Merlini, L., Rosa, M. A., Perrone, M., Frugiuele, J., Borghi, R., & Faldini, C. (2016). Central sensitization in chronic low back pain: A narrative review. *Journal of Back and Musculoskeletal Rehabilitation*, *29*(4), 625–633. https://doi.org/10.3233/BMR-160685

Scarpina, F., & Tagini, S. (2017). The Stroop Color and Word Test. *Frontiers in Psychology*, *8*, 557. https://doi.org/10.3389/fpsyg.2017.00557

Shulman, J., Zurakowski, D., Keysor, J., Jervis, K., & Sethna, N. F. (2020). Offset analgesia identifies impaired endogenous pain modulation in pediatric chronic pain disorders. *Pain*, *161*(12), 2852–2859. https://doi.org/10.1097/j.pain.0000000000001984

Stroop, J. R. (1936). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, *18*(6), 643. https://doi.org/10.1037/h0054651

Treede, R.-D. (2019). The role of quantitative sensory testing in the prediction of chronic pain. [Miscellaneous Article]. *Pain*. https://doi.org/10.1097/j.pain.0000000000001544

Vachon-Presseau, E., Martel, M.-O., Roy, M., Caron, E., Albouy, G., Marin, M.-F., Plante, I., Sullivan, M. J., Lupien, S. J., & Rainville, P. (2013). Acute Stress Contributes to Individual Differences in Pain and Pain-Related Brain Activity in Healthy

and Chronic Pain Patients. *The Journal of Neuroscience*, *33*(16), 6826–6833. https://doi.org/10.1523/JNEUROSCI.4584-12.2013

Vingård, E., Mortimer, M., Wiktorin, C., Pernold R P T, G., Fredriksson, K., Németh, G., Alfredsson, L., & Musculoskeletal Intervention Center-Norrtälje Study Group. (2002). Seeking care for low back pain in the general population: A two-year follow-up study: results from the MUSIC-Norrtälje Study. *Spine*, *27*(19), 2159–2165. https://doi.org/10.1097/00007632-200210010-00016

Yarnitsky, D. (2010). Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): Its relevance for acute and chronic pain states. *Current Opinion in Anaesthesiology*, *23*(5), 611–615. https://doi.org/10.1097/ACO.0b013e32833c348b

CURRICULUM VITAE / VITA